Skeletal muscle ultrasonography in nutrition and functional outcome assessment of critically ill children: experience and insights from pediatric disease and adult critical care studies

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Abstract

Evidence suggests that critically ill children develop muscle wasting, which could affect outcomes. Muscle ultrasound has been used to track muscle wasting and association with outcomes in critically ill adults, but not children. This review aims to summarize methodological considerations of muscle ultrasound, structural findings and possibilities for its application in the assessment of nutrition and functional outcomes in critically ill children.

Medline, Embase and CINAHL databases were searched up until April 2016. Articles describing skeletal muscle ultrasound in children and critically ill adults were analyzed qualitatively for details on techniques and findings.

Thickness and cross-sectional area of various upper and lower body muscles have been studied to quantify muscle mass and detect muscle changes. The quadriceps femoris muscle is one of the most commonly measured muscles due to its relation to mobility, and is sensitive to changes over time. However, the margin of error for quadriceps thickness is too wide to reliably detect muscle changes in critically ill children. Muscle size and its correlation with strength and function has also not yet been studied in critically ill children. Echogenicity, used to detect compromised muscle structure in neuromuscular disease, may be another property worth studying in critically ill children.

Muscle ultrasound may be useful in detecting muscle wasting in critically ill children, but has not been shown to be sufficiently reliable in this population. Further study of the reliability, and correlation with functional outcomes and nutritional intake is required before muscle ultrasound is routinely employed in critically ill children.

Introduction

Skeletal muscle wasting has been demonstrated to be a debilitating consequence of critical illness in adults, resulting in long-term impairment of function[1, 2]. Preliminary evidence suggests that muscle wasting also occurs in critically ill children, which could affect intensive care unit course, or long-term growth and development in children[3, 4]. Identification of muscle wasting would thus be important in critically ill children, so as to be able to appropriately target optimal nutritional and physical interventions to reduce muscle wasting and risk of poor outcomes in these high-risk children.

However, identifying muscle changes can be challenging in clinical practice. Current methods available such as mid-arm circumference may not accurately reflect muscle changes, while other methods such as computerized tomography (CT) or magnetic resonance imaging (MRI) are not easily conducted at bedside [5, 6]. Recently, ultrasonography has been used in adult critical care to visualize abnormalities and changes in muscle throughout the course of the intensive care unit stay[2, 7, 8]. Ultrasonography, an imaging technique that utilizes reflections of high frequency sound waves directed at tissues, is non-invasive, fast, cost-effective, and has been suggested as a possible nutrition assessment tool in critically ill adults[9]. Muscle ultrasound enables early detection of skeletal muscle wasting, which is associated with histological changes in muscle as well as functional impairment in adults[7, 8]. Muscle ultrasonography has also traditionally been used to quantify and qualify muscle morphology in pediatric populations, especially children with neuromuscular diseases[10, 11]. Muscle ultrasound would thus be a useful tool for detection of muscle wasting in nutritional practice and research, avoiding the need for complex methods in studying skeletal muscle turnover.

Several questions need to be addressed before muscle ultrasonography can be used clinically in critically ill children. They include the ideal muscle(s) for measurement, technique, time-course, echogenicity and reliability and validity of muscle ultrasound. This review aims to explore the techniques and observed patterns of muscle ultrasonography in various pediatric populations, as well as factors for consideration in muscle ultrasonography of critically ill children with the incorporation of adult critical care literature.

Methods

Searches were performed in Medline, Embase and cumulative index to nursing and allied health literature (CINAHL) databases from the earliest possible date up to April 2016. The following key words and major subject headings were used: “skeletal muscle”, “muscular diseases”, “myopathy”, “muscle atrophy”, “muscle hypertrophy”; and “ultrasonography”, “echography”. Articles were filtered for those pertaining to humans aged 0-18 years. An additional search was made using the same keywords in addition to the following: “critical illness”, “intensive care”, without an age limit. Articles unrelated to limb skeletal muscle (e.g., studying nerve, tumors or heart), using muscle ultrasound for therapeutic purpose, or using ultrasound to guide needle biopsies or injections were excluded. Shortlisted articles were reviewed qualitatively for information including ultrasound machine settings and techniques, muscle groups measured, reliability and validity, and muscle ultrasound findings with consideration for the pediatric critical illness population.

Muscle groups

A necessary first step is identification of the most appropriate muscle group. A variety of body sites have been studied in children, the most common of which include the quadriceps[12-16], gastrocnemius[17], tibia[15, 18], biceps[15, 16, 19] and forearm[15] (**Table 1**). Muscles are studied either individually (e.g., rectus femoris) or in combination with others (e.g., rectus femoris and vastus intermedius) in single or various limbs[15, 16, 20, 21].

Using a variety of muscle groups allowed for a more comprehensive assessment of whole-body nutrition assessment of children, which required ultrasound measurement of both fat and muscle layer thickness (MLT) at nine sites, including anterior and posterior upper and lower limbs, subscapular and abdominal areas[21, 22]. Equations using these measurements produced fat and muscle mass estimations comparable to that measured using more sophisticated imaging methods such as MRI and dual-energy x-ray absorptiometry (DXA)[21, 22].

A combination of distal and proximal upper and lower limb muscles have also been used in the diagnosis of neuromuscular diseases, such as Duchenne muscular dystrophy (DMD) and spinal muscular atrophy (SMA) type 1[15, 18]. Thickness of biceps brachii, quadriceps femoris, forearm flexors and anterior tibia can be compared to normative values that have been established in children aged 0-12 years [12, 16, 20, 23]. MLT is typically expected to be smaller in neuromuscular disease due to muscle atrophy or myopathy, although this varies with type of disease[10, 12, 18, 24]. Some studies have shown that thickness of the quadriceps muscle,

but not that of biceps, forearm or tibia, is significantly smaller in children with neuromuscular diseases (e.g., DMD, mitochondrial encephalomyopathy, SMA type 1) compared to children without such conditions[10, 18]. Within the spectrum of neuromuscular diseases, the tibialis anterior MLT was significantly lower in neurogenic compared to myopathic disorders[10]. Measuring several muscle groups may thus help with differentiation between types of disease. One exception to this is the lack of pathological muscle changes in early onset disease[25], as observed in infants with SMA type 1[12]. Quadriceps muscle and fat thickness of SMA type 1 infants were similar to that of healthy infants due to the lack of pathogenic changes in the former[12].

Measuring several muscle groups may also be useful in longitudinal monitoring of disease. In children with SMA type 1, MLT of upper and lower limbs generally decreased with age albeit at different rates, reflecting atrophy[25]. Similarly, children with DMD appear to experience uneven muscle wasting, as MLT decreased in biceps brachii muscles, but not in the forearm flexors, rectus femoris or tibialis anterior muscle[15]. Thus, in disease states where uneven change in upper and lower limb muscles is expected, monitoring of several muscles may provide more a comprehensive assessment.

However, as whole-body ultrasound measurements may require a significant amount of time, some longitudinal studies have used single limbs for ultrasound measurements. In children with cancer where reduced lean body mass could negatively affect disease outcomes[26], monthly ultrasound demonstrated changes in quadriceps thickness throughout the course of cancer therapy[14, 27]. This suggests that, unlike in diagnosis of neuromuscular disease, a single muscle group may be sufficient to monitor changes in body composition over time in certain groups of pediatric patients.

Both upper and lower body muscle wasting has been reported in critically ill children[3], and some adult data suggest that muscle wasting affects lower limbs more than upper limbs [28]. However, ultrasound studies measuring thickness of the biceps, forearm and quadriceps in critically ill adults have only described changes in average or total muscle thickness instead of thickness of individual muscles[29, 30]. The quadriceps alone has also been used to monitor muscle changes in critically ill adults. Measurements of the thickness of the rectus femoris, vastus intermedius and vastus lateralis, and cross-sectional area (CSA) of the rectus femoris on alternate days demonstrate an overall decreasing trend in the first 10 days of critical illness[2, 8].

The quadriceps is the most commonly studied lower limb muscle in children, of which the rectus femoris appears to be easier to visualize than the vastus intermedius in severe muscle disease due to the attenuation of ultrasound waves reaching lower muscle layers by overlying abnormal muscle[10, 15].

Together, these data suggest that in critically ill children, longitudinal measurements would be necessary to capture muscle change throughout intensive care unit (ICU) stay, possibly in more than one limb. Considering that critically ill children are usually sedated and supine, ultrasound of the anterior compartment muscles such as the quadriceps, biceps and forearms are likely easier than posterior compartment muscles such as the gastrocnemius and triceps. However, if only a single limb measurement is possible, that of the quadriceps may be suitable.

Measurement techniques

Several measurement techniques have been used in muscle ultrasonography, although most emphasize consistent transducer settings and placement, body site and subject positioning between subjects and time-period[16]. Two-dimensional B-mode ultrasound scans are usually conducted using a linear transducer ranging from 5-12 MHz[14, 16, 17] at a frequency of 25 Hz[17, 31]. Gain (i.e. intensity or brightness) settings range from 70-86 dB[15, 16], and depth is adjusted to visualize the bone depending on the age of the patient[17].

Quadriceps measurements are commonly taken at the midpoint of the anterior superior iliac spine to the superior aspect of the patella[15, 16], although adult studies have use two-thirds the distance from the anterior superior iliac spine[2, 8]. The latter allows visualization of the entire muscle in adults and larger children, which is necessary for measuring rectus femoris CSA. For the other muscles, ultrasound measurements have been taken at varying distances along the limb, and there appears to be little standardization[19, 20]. In children with dynamic growth, ultrasound landmarks using proportions of total limb length instead of absolute distance may be more appropriate, so as to account for varying changes in limb length.

Recommended patient positioning varies for different muscle groups[32]. The patient is usually positioned prone or supine or, for some young children, sitting in their caregiver's lap[24, 33]. The leg may be flat and relaxed [16] or partially flexed [33], while upper limbs are allowed to relax by the side of the body [32]. The transducer is placed perpendicular to the long axis of the muscle to be measured, with the probe angled to

optimize bone echo[15]. A generous amount of contact gel is used to minimize compression of the subcutaneous tissue and muscle[23]. Still transverse images are taken, usually in triplicate, and MLT or CSA is measured using electronic calipers (**Figure 1**)[10, 34]. Patient cooperation is also necessary in children who are conscious, otherwise MLT is likely to be inaccurately increased with contraction in children who are not relaxed[23].

Time-course

The timing of measurement would depend on the sensitivity of ultrasound in detecting changes in muscle size and echogenicity over time. Adult protocols specify measurements every 1-3 days within the first 5-10 days of ICU admission to be able to capture acute muscle changes within the initial stages of critical illness[2, 8, 29, 30], but whether this appropriately captures muscle changes in children needs to be explored as children may experience different metabolic responses from adults[35-37]. Standardization of these parameters would also help with reproducibility and comparison across studies.

Reliability and validity

Reliability

Ultrasound MLT and CSA of the lower limbs have been shown to have good intra-observer reliability in healthy and CP children, with intra-class correlation coefficients (ICC) of approximately 0.93-0.99 in children with CP, and ≥0.98 in healthy children[34, 38]. A study comparing MLT ultrasound in experienced sonographers and clinicians without prior ultrasound experience (e.g., nurses, doctors, dietitians) in healthy adults also showed good inter-observer reliability (ICC 0.95, mean difference -0.028cm, 95% confidence interval -0.067 to -0.011, p=0.1607)[39]. Similar findings have been reported in critically ill adults, with ICCs of 0.915-0.976[40, 41] and coefficient of variance <2%[42, 43].

However, in critically ill infants and young children, ultrasound MLT appears to have low reliability. Measurements of rectus femoris thickness showed good inter-observer reliability with an ICC of 0.98 and median absolute variability of 0.07cm (interquartile range 0.032 - 0.19 cm)[44]. Unfortunately, the intra-observer variability for MLT was larger than the expected decrease (95% confidence interval: 0.39cm *vs.* expected 20% decrease: 0.33cm), which limited its reliability and accuracy in the pediatric population[44].

This is, to the best of our knowledge, the only published study on muscle ultrasound in critically ill children. Although it was a mixed adult and pediatric study, there were substantial pediatric numbers (n=30), suggesting a need to re-evaluate the use of MLT in critically ill children. One possible area for further investigation in critically ill children is the reliability of muscle CSA, which has a lower coefficient of variation and thus an advantageous signal to noise ratio compared to MLT in the measurement of muscle wasting[34, 45].

Concurrent validity – comparison to gold standards

Muscle ultrasound has been compared to more specialized muscle imaging methods. In children with malignancy, MLT using ultrasound and CT scans showed little variability between the two methods – ICC was 0.99 and 0.98 respectively for biceps and quadriceps MLT[46]. Muscle ultrasound measurements have not been compared to more specialized imaging methods in critically ill adults, although in healthy adults, ultrasound and MRI measurements of shoulder MLT and leg CSA are strongly correlated with low coefficient of variation (1.7-3.1%)[47, 48].

Content Validity – reflection of whole-body nutritional status

MLT of the arm, trunk, thigh and lower leg has been used to reliably calculate total skeletal muscle volume as measured by MRI in healthy pre-pubertal children[21]. Compared to MLT, CSA proved to be a better estimator of gastrocnemius volume determined by MRI in children with CP (r^2=0.858-0.903 *vs.* 0.779-0.831)[49]. In critically ill adults, quadriceps MLT has been compared with muscle CSA at the third lumbar vertebra (L3) obtained from CT scans – an indicator of total body muscle mass[50, 51]. Yet, quadriceps MLT was only moderately correlated with L3 muscle CSA (r=0.45, p<0.001), possibly confounded by varying tissue edema and compressibility[51].

Nevertheless, ultrasound appears to be more sensitive than weight in assessing muscle changes. Children with leukemia had decreasing quadriceps MLT with a simultaneous increase in subcutaneous fat during the course of treatment (approximately 2-3 months), resulting in no obvious change of total limb circumference or weight[14]. Annual quadriceps ultrasound of children with moderate or severe CP aged 6-16 years (n=26) also demonstrated that progressive weight gain was correlated with increases in fat and

not muscle[13]. Muscle ultrasound may thus be advantageous to current nutritional assessment tools in differentiating between muscle and fat changes.

Muscle ultrasound has also been explored for its association with nutritional intake within the ICU. In critically ill adults, ultrasound changes in total MLT of the forearm, biceps and quadriceps do not appear to correlate with energy intake[30], while ultrasound rectus femoris CSA unexpectedly decreased with greater protein provision[2]. Such associations have not yet been established in critically ill children. Future studies to do so would contribute greatly to the utility of muscle ultrasound as a nutrition assessment tool in these patients.

Predictive validity – functional outcomes

Muscle wasting can lead to long-term functional impairment[1], and ultrasound vastus intermedius MLT and rectus femoris CSA has been associated with muscle function in critically ill adults[8]. Pediatric ultrasound studies suggest some association between muscle size and function in children. In healthy children (aged 0-16 years), MLT corresponded with strength measured by dynamometry in the quadriceps, tibia, biceps and forearm[20]. Similarly, gastrocnemius muscle volume, vastus lateralis thickness and quadriceps thickness were associated with gross motor function measures (Gross Motor Function Classification System, Gross Motor Function Measurement-66 and Pediatric Evaluation of Disability Inventory) and strength in children with CP[17, 33, 52]. Conversely, in a group of pre-pubertal and early pubertal boys (7-12 years), CSA of elbow and knee extensors and flexors was not associated with strength of the arm and leg muscles[53]. With progressive functional training, quadriceps MLT and rectus femoris CSA, but not gastrocnemius thickness, increased in ambulatory CP children aged 5-10 years[54]. Post-training muscle size was also not significantly correlated with mobility or motor function[54].

This suggests that muscle size may not necessarily increase with resistance exercise, or reflect strength gains in children[53, 55]. Muscle hypertrophy is hypothesized to occur only during puberty in the presence of androgens[56]. In pre-pubertal children, electromyogram studies have suggested that greater strength may due to neural adaptation instead, such as enhanced motor unit recruitment and firing rate of motor units[57].

Given the functional impairment reported in pediatric critical care survivors[58], ultrasound of lower limb muscles may be useful in detecting strength deficits in children. However, the relationship between muscle

size and strength or function does not appear consistent in children, and requires further study. Interestingly, a pilot study in adult ICU survivors (n=11) requiring ≥7 days of mechanical ventilation also demonstrated a lack of correlation between muscle size and strength at 6 months[59]. Despite normalization of muscle mass, 3 patients experienced persistent muscle weakness, the reason for which is still unknown[59]. Changes in muscle CSA should thus be interpreted in caution in children (especially pre-pubertal) and perhaps accompanied by muscle strength evaluation.

Echogenicity

Echogenicity, i.e. the presence of white areas or brightness, is another property that has been studied in muscle ultrasonography. Echogenicity indicates the presence of fat or fibrous tissue infiltrates[60] or the inflammation of muscle[61]. Assessment of the extent and pattern of echogenicity and inhomogeneity (e.g. fine *vs.* coarse grained) of the muscle and the loss of bone echo can provide some indication of muscle quality[62]. Some technical considerations include the standardization of gain settings across subjects and time points to avoid an artificial increase or decrease in echogenicity. The use of calibrated muscle backscatter is also currently being studied in an effort to standardize echogenicity across different machines[63].

Echogenicity can be interpreted qualitatively, semi-quantitatively and quantitatively. Qualitative assessment is usually conducted by an experienced sonographer who determines ultrasound findings to be normal, myopathic, neurogenic, etc[11]. To improve objectivity and accuracy, the semi-quantitative 4-point Heckmatt score is used, based on a visual assessment of the muscle and bone [64]. A grade I ultrasound is considered normal, while a grade IV indicates a complete loss of bone echo and very strong muscle echo [64]. Finally, histogram-based gray-scale analysis, or quantification of the frequency and size of gray-scale pixels in an image, improves sensitivity and specificity further [18] (**Table 2**). This can also be obtained using commercially available (e.g., Adobe Photoshop software, Adobe Systems Incorporated, USA) or specialized computer software[7, 15, 16, 19].

Echogenicity remains relatively constant with age in healthy children [20], and increases with age in progressive neuromuscular disease[12, 15, 65, 66]. Echogenicity is thus used in the diagnosis of neuromuscular disease and in the differentiation between myopathic and neurogenic disease[11]. In myopathy (e.g., DMD)

the echogenicity is fine, granular and homogeneous with loss of bone echo[11], while in neurogenic disease (e.g., SMA type 1) the echogenicity is inhomogeneous, patchy and streaked (**Table 1**)[11, 32]. A third echogenicity pattern has been reported in inflammatory muscle disease, which involves echogenic muscle with preserved bone echo [32].

Echointensity has been associated with function, although not consistently so. In patients with DMD and ambulant children with CP, muscle echogenicity was associated with worsening ambulation, function and strength[15, 67]. However, the association between echointensity and mobility was no longer apparent in non-ambulant children with CP[67]. In healthy children aged 0 – 12 years, echointensity of the biceps, but not the quadriceps, tibia or forearm, was associated with muscle force [20]. This mirrors the inconsistencies found between muscle size and strength or function.

In critically ill adults, ultrasound echogenicity is indicative of myopathy, increasing with length of stay until a homogenous, ground-glass appearance is seen with loss of bone echo by day 14 of ICU stay[8, 40]. Increased echogenicity also corresponded with myofiber necrosis and fascial inflammation found on muscle biopsy of critically ill adults[7]. Using muscle echogenicity as an indicator of compromised muscle quality may thus be a feasible option in critically ill children. However, there is first a need to determine the degree of muscle changes in critically ill children, as mild necrosis may not show a significant difference in echointensity. There is also a need to establish whether echogenicity reflects muscle strength and function in critically ill children.

Limitations of skeletal muscle ultrasonography

There are several advantages of muscle ultrasonography in critical illness. Current methods of identifying changes in body composition in children such as weight, limb circumference and skinfold thickness may not be able to accurately detecting muscle changes within the intensive care unit [5] (**Table 3**). Bioelectrical impedance analyses are unreliable in altered hydration states, which are common in the critically ill patient [68]. Muscle biopsies and “gold standard” imaging methods that emit radiation such as CT or MRI scans are ethically difficult in a pediatric population, especially in research settings. In comparison, muscle ultrasound is a relatively inexpensive, non-invasive, child-friendly tool in muscle imaging. The ease of teaching, bedside convenience and fast results make it widely applicable to clinical and research settings. The non-

volitional nature also allows for early detection of muscle wasting in children who are often unconscious or too young to follow commands.

However, there are similarly many limitations of muscle ultrasound in critically ill children. Firstly, the reliability of muscle ultrasound in detecting changes within the pediatric ICU need further study. The inter and intra-observer reliability, and the accuracy of muscle ultrasounds in patients with edema, patients with only mild myopathic changes, or in young children who are struggling or uncooperative are some practicality issues that need to be addressed. Studies exploring reliability of muscle CSA as well as quantitative echogenicity in critically ill children have yet to be published in the pediatric population.

Considerations for whom to perform the muscle ultrasound may also be relevant – doctors, nurses, physiotherapists and dietitians are likely bedside operators for the assessment of a critically ill child. Although operators without previous experience can be reasonably trained in ultrasonography measurement of MLT and echogenicity[39, 65], ultrasound remains highly operator dependent. Standardization of ultrasound settings, sufficient training and operator reliability tests would be important to increase the clinical utility of muscle ultrasound in critically ill children.

Our review is limited in that it was not a systematic review, and may be prone to selection bias. However, as the purpose of this review was to determine the applicability and techniques of muscle ultrasound in critically ill children, a systematic review would have limited applicability given the scarce studies available in this population.

Conclusions and future directions

Currently, there is a lack of studies investigating the use of muscle ultrasound in critically ill children. Evidence from critically ill adults and non-critically ill pediatric populations suggests that muscle ultrasound is a useful, non-invasive tool to detect changes in muscle size. For practical reasons, anterior component muscles appear most feasible for measurement, of which the quadriceps has been most commonly studied. Longitudinal measurements of either upper and lower limbs, or quadriceps alone, may help with monitoring muscle changes during critical illness.

However, muscle thickness measurements have not been demonstrated to be reliable in critically ill children. Further studies of the reliability and validity of muscle size and echointensity via ultrasound, as well as standardization of techniques are required before it can be used routinely in critically ill children. Subsequent study on the association between muscle changes and functional ability as well as nutritional intake would further increase the utility of muscle ultrasound as a nutritional and functional assessment tool in critically ill children.

Statement of Authorship

All authors contributed to the design of the manuscript, critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Table 1. Muscle ultrasound size and echogenicity findings in pediatric populations

Population	Muscle or fat thickness	Echogenicity
Healthy children [12, 19, 20, 23, 53]	• MLT (biceps brachii, forearm flexors, quadriceps femoris, tibialis anterior) increases with age, muscle to subcutaneous fat ratio range 1:1 to 3:1 • MLT and CSA (elbow and knee flexors and extensors) correlated with muscle force measured by dyanometry in teenage, but not pre-pubertal boys	• Echointensity remains constant with age
Muscular dystrophy [15, 65, 66, 69]	• MLT (biceps brachii, forearm flexors, quadriceps femoris, tibialis anterior) is comparable to healthy children, decreases or remains the same with age	• High homogeneous echointensity • Increases with age and disease progression • Correlates with immobility
Spinal muscular atrophy [12, 24, 25, 69]	• MLT may be normal in early infancy, may decrease with age and be lower than healthy infants • Subcutaneous fat thickness higher than normal, increases with age • Muscle to subcutaneous tissue ratio reduced (1:1 or lower) compared to healthy infants	• May be normal in infancy, increases rapidly with age • Inhomogenous, patchy increase in echointensity
Cerebral palsy (CP) [13, 17, 31, 33, 34, 49, 52, 54, 67, 70]	• Gastrocnemius MLT similar to healthy children until 15 months of age, thereafter lower than healthy children • Gastrocnemius muscle volume lowest in immobile children with CP • Rectus femoris CSA, rectus femoris and vastus lateralis thickness lower than healthy children • Vastus lateralis thickness predictive of strength in immobile and mobile children with CP • Quadriceps MLT significantly differs with level of motor function across subjects • Quadriceps MLT and rectus femoris CSA increases with progressive functional training	• Higher than healthy children • In ambulatory children with CP, increases with worsening motor function • Does not increase with age
Oncology [14, 27]	• Decrease in quadriceps MLT peaked at 4 – 6 weeks of cancer therapy in children with acute lymphoblastic leukemia, returned to pre-therapy levels by 24 weeks • Fat thickness increased with simultaneous decrease in MLT • In some children with solid tumors and leukemia, quadriceps MLT was already reduced at diagnosis while traditional anthropometry was comparable to healthy children	Nil
Mitochondrial disorders [11, 71]	• MLT (biceps brachii, forearm flexors, quadriceps femoris, tibialis anterior) in children mitochondrial disorders comparable to healthy children	• May be higher than healthy children • May not correlate with severity of symptoms or muscle infiltrates
Juvenile dermatomyositis [11, 61, 72]	• MLT decreased over time after treatment (possibly due to reduction in muscle edema)	• May be increased in acute inflammation (inconsistent evidence) • May be decreased by muscle edema
Critically ill children [44]	• MLT showed acceptable inter-observer variability, but unacceptable intra-observer variability	Nil

CSA: cross sectional area; MLT: muscle layer thickness

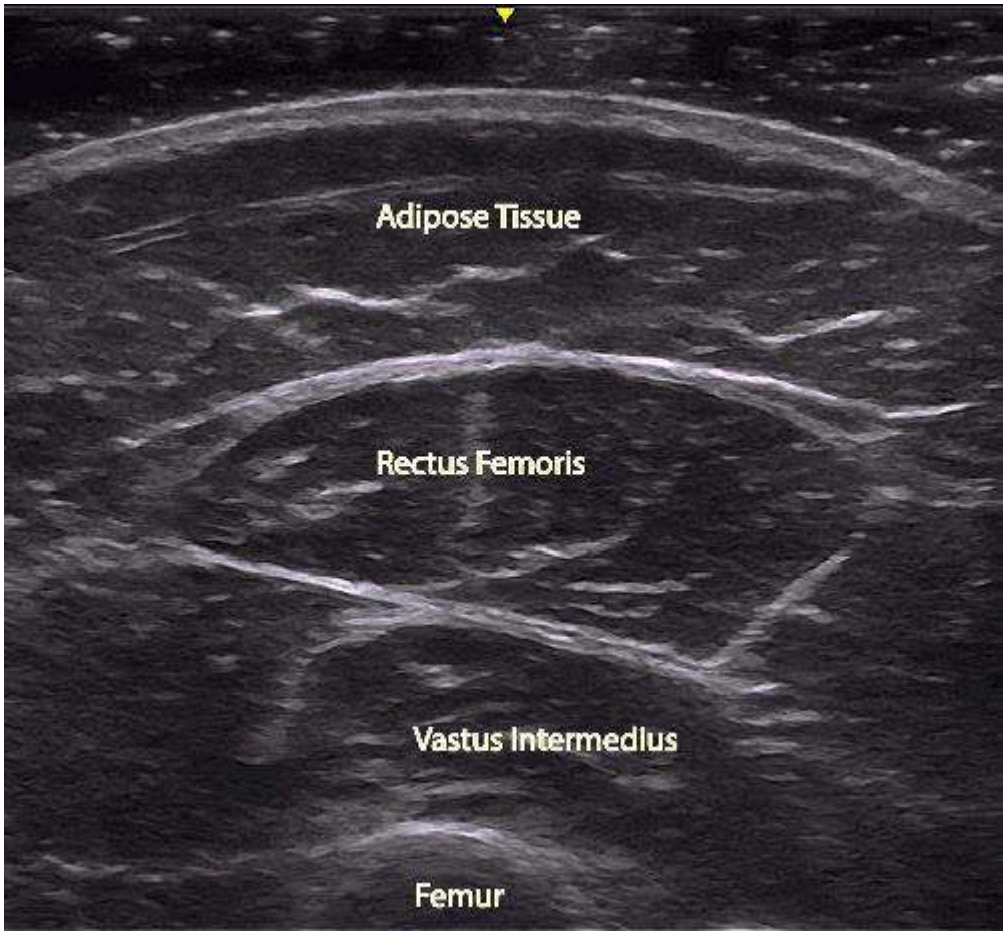
Table 2. Sensitivity and specificity of muscle ultrasound echointensity in diagnosing neuromuscular disease

Method	Classification used	Compared against	Sensitivity	Specificity
Qualitative [11]	Visual assessment (myopathic, neurogenic, abnormal, etc.)	Biochemical/ genetic evaluation, biopsy	81%	96%
Semi-quantitative [62]	Heckmatt criteria ≥ grade 2	Electromyogram (EMG), biochemical/ genetic evaluation, biopsy, clinical evaluation	71%	92%
Quantitative [18, 62]	Gray-scale analysis: z-score of ≥0.9 in three or more muscle groups	EMG, biochemical/ genetic evaluation, biopsy, clinical evaluation	87 – 92%	67 – 90%
Quantitative [10]	Gray-scale analysis: z-score >3.5 in one muscle or >2.5 in two muscles or >1.5 in three muscles	EMG, biochemical/ genetic evaluation, biopsy, clinician diagnosis	71%	91%

Table 3. Methods used to identify muscle mass and muscle changes in the intensive care unit

	Advantages	Limitations
Bioelectrical impedance	Fast, conducted at bedside, relatively cost-efficient	Unreliable in altered hydration states
Computerized tomography, magnetic resonance imaging	Precise, accurate, able to accurately detect low muscle mass in healthy populations	Costly; substantial dose of radiation
Dual-energy X-ray absorptiometry	Precise, accurate	Only able to identify lean body mass (does not differentiate between organs and skeletal muscle); costly; unable to detect small changes (3-5%) in muscle
Muscle biopsy	Shows histological changes in muscle	Invasive process
Skinfold thickness and muscle arm circumference	Fast, conducted at bedside, relatively cost-efficient	Difficult to perform in recumbent patients; high operator variability; affected by edema
Ultrasound	Fast, conducted at bedside, relatively cost-efficient	Operator-dependent; affected by edema

Figure 1. Ultrasound image of the quadriceps muscles



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